

Cervical cancer and low-risk HPV; a case report

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Summary

A case of cervical cancer in a 32-year-old woman with a genotype 6 HPV genital infection that developed from a cervical low-grade SIL after a LLETZ procedure two years before is presented.

This case obliges us to reconsider both the benign nature of low-grade lesions and the potentially good prognosis of low-risk HPV infection.

Key words: Cervical cancer; Low-grade; Low-risk; HPV infection; Genotype 6.

Introduction

In recent years a significant number of studies have appeared in the literature [1-6] linking human papillomavirus (HPV) infection with cervical cancer and its precursor lesions. This has made it possible to establish HPV infection as an important risk factor associated with cancer of the uterine cervix. It has been observed that the risk increases according to the type of HPV; types 16 and 18 have the highest risk (OR = 138.1 and OR = 92.3, respectively), while others with a lower risk are types 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66 and 68 [7]. Some types are only rarely found in association with invasive cervical cancer (types 6, 11, 42, 43 and 44).

A case of invasive cervical cancer in a young woman with a history of a low-grade squamous intraepithelial lesion (SIL) and HPV genotype 6 infection is presented.

Case Report

The patient, 30 years of age, was seen for condylomas of the vulva and uterine cervix, and a cytological diagnosis of low-grade SIL. She had no relevant family history of illness, and her own medical history included appendectomy, tobacco use (1 pack of cigarettes per day) and occasional use of hashish and cocaine. Menarche occurred at age 11, and her menstrual cycles were regular. She began to have sexual relations at age 16, and used no birth control methods. At age 23 she had an abortion, and had not had a routine gynecological examination during the previous seven years.

On gynecological examination, an irregular nodular lesion was observed on the left labia majora that was suggestive of condyloma, and through the speculum, exophytic lesions were observed on the uterine cervix and in the vagina that also appeared to be condylomas. Colposcopic examination showed a large mosaic lesion highly suggestive of condyloma. Cervico-vaginal cytology and a cervical biopsy were performed. HPV detection and genotyping were performed using the polymerase chain reaction (PCR) technique and subsequent hybridization using probes specific to the most common genotypes of human

papillomavirus. The cytology results showed low-grade SIL, "clue cells" suggesting bacterial vaginosis and cellular changes suggestive of HPV infection; the results of PCR showed HPV genotype 6. The results of the cervical biopsy indicated acuminata condyloma.

Following a 7-day treatment with vaginal clindamycin, the patient underwent vaporization of the vulvovaginal condylomas and LLETZ (large loop excision of transformation zone) on an outpatient basis in September 2003. In postoperative follow-up the vulvovaginal and cervical condylomas had disappeared, and the result of histological analysis of the specimen obtained by LLETZ was low-grade squamous intraepithelial lesion and multiple condylomas. Six months after the LLETZ procedure, the cytology results of a vaginal smear showed inflammation as a result of trichomonas vaginalis, which was treated with a single 2 g dose of oral metronidazol. Colposcopy was normal. Six months later the cytology was repeated, and the results showed high-grade SIL. Cone biopsy and endocervical curettage were performed in February 2005 to confirm the diagnosis. The histologic diagnosis of the cone biopsy specimen was infiltrating squamous carcinoma 9 mm in length and 4 mm deep and extensive high-grade SIL affecting the surgical margin. Endocervical curettage also revealed the presence of high-grade SIL.

A preoperative magnetic resonance imaging (MRI) study showed the lesion affecting only the cervix.

In order to preserve the patient's fertility, it was suggested that she undergo a trachelectomy. After the pros and cons were explained to her, she agreed to the procedure.

The LLETZ and cone biopsy specimens were subjected to a microarray-based method (Genomica[®]) for the detection of HPV. Only the existence of genotype 6 was confirmed.

Discussion

This is a rare case of squamous carcinoma of the cervix in a young woman infected with HPV genotype 6. The following is a discussion of the risk factors presented by the patient and a review of the relevant literature.

Among the risk factors for cervical carcinoma is sexual activity at an early age; in this case, at 16. It has been observed that women who begin having sexual relations after age 20 have a lower risk of developing cervical

cancer than those who begin earlier [8]. The patient reported smoking one pack of cigarettes per day (approximately 20 cigarettes). Some studies [9] have shown that women who smoke are at greater risk for developing cervical cancer than non-smokers (RR = 3.0). These results are supported by the finding that the concentration of nicotine and cotinine is higher in the cervical mucosa than in the blood. Nicotine is thought to inhibit growth factor degradation at the lysosomal level, and increase chromatin accumulation of the non-degraded platelet derived growth factor [10].

According to the data collected by Benedet *et al.* on the results of treatment in gynecological cancer [11], the average age of the appearance of cervical cancer is 51.4 years, between 8 and 20 years later than the age of onset of in situ carcinoma [12]. In our case, the patient was a 32-year-old woman diagnosed with infiltrating squamous carcinoma, Stage IA2.

It is noteworthy that in a period of less than two years following diagnosis of low-grade SIL by large loop biopsy of the transformation zone (LLETZ), during which cytological and colposcopic testing was performed every six months, the lesion developed from low-grade SIL to infiltrating squamous carcinoma. This is surprising in light of reports in the literature indicating that just 11% of low-grade lesions progress to high-grade SIL, and only 1% become invasive carcinomas [13].

As in our case, other studies have observed that both condylomas and low-grade SIL are associated with type 6 HPV infection [14, 15].

The frequency with which HPV genotype 6 is isolated in women with cervical cancer is very low. In a meta-analysis of 85 studies in which PCR was used to estimate the prevalence of HPV infection [16], of a total of 10,058 cases of cervical cancer, the mean frequency of HPV genotype 6 detection was 0.5%, ranging between 0 and 8%, although in some studies in which a higher frequency was observed, it is possible that other high-risk HPV genotypes were present but undetected.

In our case, the presence of HPV infection was detected using two PCR techniques that make it possible to identify co-infections and a broad spectrum of genotypes: "Line Probe Assay" (LIPA, Innogenetics Laboratories®), which makes it possible to identify up to 25 different HPV genotypes in a single cervical smear; and a microarray-based method (Genomica®) specific to the 35 most prevalent HPV genotypes (3, 6, 7, 11, 16, 18, 26, 31, 33, 35, 39, 40, 42, 43, 44, 45, 51, 52, 53, 54, 56, 58, 59, 61, 62, 66, 68, 70, 71, 72, 81, 82, 83, 84, 85, 89) performed on the LLETZ and cone biopsy specimens.

This case obliges us to reconsider both the benign nature of low-grade lesions and the potentially good prognosis of low-risk HPV infection, as other authors have also noted [17], and suggests that women presenting with low-grade SIL should be followed closely, independently of whether they present with HPV infection by a low-risk genotype.

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